The clinical and electrophysiological spectrum of cardiac sodium channel mutations
Smits, J.P.P.

Citation for published version (APA):
Smits, J. P. P. (2004). The clinical and electrophysiological spectrum of cardiac sodium channel mutations

General rights
It is not permitted to download or to forward/distribute the text or part of it without the consent of the author(s) and/or copyright holder(s), other than for strictly personal, individual use, unless the work is under an open content license (like Creative Commons).

Disclaimer/Complaints regulations
If you believe that digital publication of certain material infringes any of your rights or (privacy) interests, please let the Library know, stating your reasons. In case of a legitimate complaint, the Library will make the material inaccessible and/or remove it from the website. Please Ask the Library: http://uba.uva.nl/en/contact, or a letter to: Library of the University of Amsterdam, Secretariat, Singel 425, 1012 WP Amsterdam, The Netherlands. You will be contacted as soon as possible.

UvA-DARE is a service provided by the library of the University of Amsterdam (http://dare.uva.nl)
CHAPTER 3.1

THE BRUGADA SYNDROME
3.1.1 Introduction

The Brugada syndrome is an important cause for malignant ventricular tachyarrhythmias and sudden cardiac death (SCD) in patients without any evidence of structural heart disease or systemic disease affecting the heart.\(^1\) The syndrome is characterized by J-wave and ST segment elevation in the right precordial leads (V1 to V3). The J-wave elevation may give the QRS complex the appearance of a right bundle branch block (Figure 1). Brugada et al. were not the first to describe this abnormal ECG\(^5\) they were however the first to recognize that individuals with this ECG are at increased risk for SCD.\(^1\)

The Brugada syndrome is an inherited disease; this was already recognized in the original report of Joseph and Pedro Brugada et al. in 1992 and has since then been convincingly established and proven in 1998 by linking the syndrome to mutations in the \textit{SCN5A} gene.\(^6\)

The \textit{SCN5A} gene on chromosome 3p21 encodes the pore forming \(\alpha\)-subunit of the cardiac sodium channel (hH1).\(^6,7\) Brugada syndrome causing mutations on this gene have consistently shown to reduce cardiac sodium current.\(^8\) The fact that \textit{SCN5A} encodes a cardiac ion channel and that the resulting reduction in depolarising sodium current can theoretically explain the Brugada syndrome have led to the theory that the Brugada syndrome is an ion channel disease.\(^6,8\)

If this is true for all Brugada syndrome cases remains to be proven because in only 15-30\% of Brugada syndrome cases and families a mutation in the \textit{SCN5A} gene is identified.\(^9,10\) In one family the syndrome has been linked to another locus on chromosome 3, 3p22-25,\(^11\) but the affected gene that is encoded by this region awaits identification. In the remaining cases of Brugada syndrome no responsible gene or chromosome has been identified yet although many of them are familial.\(^4\)

3.1.2 Clinical characteristics and diagnostic criteria

The Brugada syndrome as a clinical entity is 10 years old and diagnostic criteria still need fine-tuning. Recently a consensus report from a special Arrhythmia Working Group of the European Society of Cardiology was published attempting to establish consensus on diagnostic criteria.\(^12\) With better understanding of the pathophysiology of the disease and development of new and better diagnostic techniques these criteria may change over time.

3.1.2.1 Diagnosis and risk stratification

Several diagnostic tools are important in the Brugada syndrome. Besides a diagnostic purpose some tools have an additional role in risk stratification. In the following section we will discuss the diagnostic process in patients suspected to have Brugada syndrome.
3.1.2.2 Patient and family history

The history of a suspected Brugada syndrome patient may reveal symptoms from cardiac arrhythmias such as syncope. Similar symptoms and SCD may have been present in the patients family and have to be asked for. A complete list of drugs used by the patient should be recorded. Thorough physical and laboratory examination of a suspected Brugada syndrome patient should exclude the presence of cardiac and systemic diseases or electrolyte disorders that may alternatively explain the Brugada syndrome features.

The 12 lead ECG is usually the first indication for the diagnosis and shall therefore be discussed separately. The typical ECG may be transient and from time to time be completely normal.\(^9\)\(^12\) Therefore suspected patients should be challenged using class Ic antiarrhythmic drugs, as shall also be discussed seperately.\(^12\)\(^-\)\(^17\) Further diagnostic tests required are a normal chest radiograph, echocardiography, blood electrolytes, glucose and other standard laboratory tests. Additional investigations that may be helpful are a stress test, nuclear magnetic resonance imaging (MRI), clinical electrophysiological testing (EPS) and tissue biopsy of the heart. Coronary angiography may be usefull in patients when myocardial ischemia is
suspected. Other diseases that must be excluded if clinical suspicion exists can be both cardiac and non-cardiac (Table 1).

Table 1. Cardiac and non-cardiac abnormalities that can cause ST-Segment elevation in the right precordial leads

<table>
<thead>
<tr>
<th>Cardiac</th>
<th>Non-cardiac</th>
</tr>
</thead>
<tbody>
<tr>
<td>Right or left bundle branch block, left ventricular hypertrophy</td>
<td>Dissecting aortic aneurysm</td>
</tr>
<tr>
<td>Acute myocardial ischemia or infarction</td>
<td>Acute pulmonary thromboemboli</td>
</tr>
<tr>
<td>Acute myocarditis</td>
<td>Various central and autonomic nervous system abnormalities</td>
</tr>
<tr>
<td>Right ventricular ischemia or infarction</td>
<td>Heterocyclic antidepressant overdose</td>
</tr>
<tr>
<td>Mediastinal tumor compressing RVOT</td>
<td>Duchenne muscular dystrophy</td>
</tr>
<tr>
<td>Arrhythmogenic right ventricular dysplasia/cardiomyopathy</td>
<td>Friedreich's ataxia</td>
</tr>
<tr>
<td>Long-QT syndrome, type 3</td>
<td>Thiamine deficiency</td>
</tr>
<tr>
<td>Early repolarization syndrome</td>
<td>Hypercalcemia</td>
</tr>
<tr>
<td>Other normal variants (particularly in men)</td>
<td>Hyperkalemia</td>
</tr>
<tr>
<td>Cocaine intoxication</td>
<td></td>
</tr>
</tbody>
</table>


3.1.2.3 The electrocardiogram

The electrocardiogram (ECG) is an important diagnostic tool in Brugada syndrome. As mentioned previously the typical Brugada ECG is characterized by J wave elevation and ST segment elevation in the right precordial leads (V1-V3). The J wave elevation may give the QRS complex in the right precordial leads the appearance of an R' in RBBB. In addition there may be signs of conduction slowing such as prolongation of PQ, QRS and His-ventricle intervals and leftward deviation of the frontal QRS axis. (Figure 1.)

Three different ST-segment shapes, type 1 to 3, are recognized. In type 1 the ST-segment in the right precordial leads has a prominent J-wave (≥2mm or 0.2mV) after which it gradually slopes down to the iso-electric line, giving the segment a coved appearance, after which a negative T-wave may follow. Type 2 shows a less prominent J-wave, but still at least 2mm or 0.2mV, that slopes down but remains above the iso-electric line (≥ 1mm) and is followed by a positive or biphasic T-wave, giving the ST-segment a saddle type appearance. Type 3
may be saddle or coved shaped as described previously but with less ST-segment elevation of \( \leq 1\text{mm} \).\textsuperscript{12} Although not specific for the Brugada syndrome, a subset of patients may be found to have slightly prolonged QT intervals.\textsuperscript{18,19} All these ECG features may be transient, which may complicate diagnosis.

If ventricular tachycardia occurs and is recorded, the ECG typically shows rapid self-terminating polymorphic tachycardia although monomorphic tachycardia has also been reported.\textsuperscript{12}

### 3.1.2.4 Drug challenge

Because the ECG features in Brugada syndrome may be transient or in case of a type 2 or 3 ECG not conclusive, patients can be tested by intravenous administration of sodium channel blocking drugs.\textsuperscript{12-17} The rationale for this test is that if indeed a imbalance between depolarizing and repolarizing cardiac ion currents is at the basis of both ST segment elevation and the arrhythmias sodium current blockade may unmask or aggravate these (Figure 2).\textsuperscript{13} According to the latest consensus report the drug challenge is to be considered positive in the following circumstances.\textsuperscript{12} When the baseline ECG shows no abnormalities the development of a J-wave amplitude of \( >2\text{mm} \) in leads V1 and/or V2 and/or V3 with or without a RBBB is considered positive. When the baseline ECG is a type 2 or 3 the conversion to a type 1 or an increase in J-wave amplitude of more than 2mm without development of a type 1 ECG is considered a positive test. Patients with a type 1 ECG should not be tested as the test has no added value and may put these patients at risk for arrhythmias. Drugs in use for the test are procainamide, flecainide and ajmaline of which the latter two are most potent.

The value of drug challenge is still disputed; sensitivity, specificity and reproducibility of the test still need to be established.\textsuperscript{12-17} An important issue that complicates this results from the fact that reports on these issues often have tested non-uniform patient groups.

During drug challenge patients are at risk for developing ventricular arrhythmias.\textsuperscript{14,15} Therefore the test should always be performed in a hospital setting with ACLS facilities available. In addition to monitoring the patient during the test for development of ventricular arrhythmias or ventricular premature complexes the QRS width should be monitored and the test should be stopped when a QRS widening of \( \geq 30\% \) occurs. The maximum flecainide dosis to be administered is 150mg.\textsuperscript{15}
3.1.2.5 Clinical electrophysiological investigation (EPS)

The value of EPS in Brugada syndrome patients is like that of flecainide challenge the subject of an ongoing debate and investigation. Sensitivity, specificity and reproducibility of this diagnostic tool in Brugada syndrome are unclear. \cite{12,9,20,21}

EPS testing in Brugada syndrome may however serve two purposes. It may have a role in diagnostics but its most important role may be expected in the assessment of the risk for a patient to development malignant arrhythmias.

The indication for EPS and the consequences of the test are depends on whether patients with a spontaneous or induced Brugada syndrome ECG are symptomatic or not.

It can be argued that symptomatic Brugada syndrome patients who have had documented VF do not need EPS testing at all because the test has neither diagnostic nor prognostic value in these patients. Testing these patients may however help gain more insight in the value of EPS and is therefore recommended. Asymptomatic patients should be tested for similar reasons. But in these patients it may additionally have a diagnostic and prognostic value. Inducibility of arrhythmias may identify a high-risk group of patients that is not symptomatic yet and probably need treatment. It is known that arrhythmias cannot always be induced in symptomatic patients. \cite{20,21} Therefore the negative predictive value of EPS needs to be clarified.

Figure 2. The flecainide challenge. ECG’s are of the same patient as in Figure 1B. (A) ECG before administration of flecainide. (B) ECG after administration of flecainide intravenously, note the increase in ST-segment elevation in leads V1-V3.
and until that matter has been clarified asymptomatic non-induceable patients probably need clinical follow up.

### 3.1.3 Risk stratification

Among individuals diagnosed with Brugada syndrome many clinical subdivisions are possible. In the previous paragraph we have already mentioned differences between symptomatic and asymptomatic individuals that are relevant in risk stratification. Further risk stratification may become possible with the longer follow up of patients. Questions in risk stratification that will need to be addressed are: is the risk to become symptomatic dependent on the genetic background of the disease and what is the role of variable penetrance? Before these questions can be answered the genetic background of the disease itself needs further clarification and what the responsible factors or genes for the variation in expression of the disease are. Thus whether the different groups, symptomatic or asymptomatic, represent different manifestations of the same disease with variability in penetrance of mutations in one gene or whether they are the manifestation of different pathophysiological mechanism(s). The clinical follow up of families and genetic screening may be helpful in answering these questions.

### 3.1.4 Family screening

When a positive family history is obtained from a patient all family members should be offered screening for the disease. Screening should consist of a baseline 12 lead ECG and/or one after flecainide challenge.

Genetic screening may be indicated for several reasons. First, if the disease in a family is causally linked to a gene, presently the only candidate is SCN5A, this may be the ultimate test to identify family members who are at risk. Second, there is a scientific indication. Genetic screening may identify novel mutations in the SCN5A gene. When it involves large families it may help identify other in Brugada syndrome involved genes using linkage analysis. This may ultimately enable establishment of a phenotype-genotype relationship in Brugada syndrome and facilitate future genetic screening which is the subject of the next chapter.

### 3.1.5 Therapy

Presently no adequate treatment for the Brugada syndrome exists. Treatment of the tachyarrhythmias in the Brugada syndrome is limited to the implantation of an ICD to terminate them when they occur. Prevention of the tachyarrhythmias by antiarrhythmic drugs is not possible although there is experimental and clinical evidence that this should be possible.
Theoretically, pharmacologic treatment of Brugada syndrome would require drugs that would increase $I_{Na}$ or $I_{Ca}$ or reduce $I_{to}$. Experimental in vitro studies using myocardial wedge preparations support this idea.\textsuperscript{22,23}

Case reports give in vivo support to these observations. These case reports concern Cilostazol\textsuperscript{24} and Quinidine.\textsuperscript{25,26} Cilostazol is a phosphodiesterase inhibitor and has clinical use as an antiplatelet drug. It has been reported to prevent ventricular fibrillation in one patient diagnosed with Brugada syndrome.\textsuperscript{24} The effects are probably due to the reported effects of Cilostazol increasing $I_{Ca}$ and decreasing $I_{to}$. Whether the drug is able to normalise the Brugada syndrome ECG features is not known. A drug that has been reported to do so, both in vitro and in vivo, is Quinidine.\textsuperscript{25,26} This type Ia antiarrhythmic vagolytic drug, that blocks $I_{to}$, has been shown to have a beneficial effect in patients with idiopathic VF among which a subset with Brugada syndrome.

The use of these drugs in clinical practice needs further evaluation. Their use and development of other drugs depend on a greater insight in the pathophysiology of Brugada syndrome. Drug treatment may eventually become dependent on the genetic background of the Brugada syndrome in individual patients.

### 3.1.6 Theoretical pathophysiological basis of the Brugada syndrome

The theoretical basis of the Brugada syndrome comes from experimental evidence on action potential differences between the endo- mid- and epicardial layers of the heart.\textsuperscript{22,23} In arterially perfused wedge preparations of canine hearts such differences have been observed and the role of contributing ion currents have been studied.

Under normal conditions the epicardial action potential in these preparations is shorter than the endocardial and shows a prominent “notch” during phase 1 of the action potential resulting from the greater presence of $I_{to}$ in this layer (Figure 3.). The shorter epicardial AP results in a voltage gradient between the epi- and endocardium responsible for inscription of the T wave on the ECG. The greater phase 1 repolarization between epi- and endocardium may be visible on the normal ECG as a J wave or an Osborn wave in case of exaggeration of phase 1 (Figure 3).

Under pathological conditions when $I_{Na}$ is reduced, as in the Brugada syndrome this will cause a reduction in action potential upstroke and overshoot in both the endo- and epicardial layer. Because the epicardium has more $I_{to}$ a reduction in inward depolarizing $I_{Na}$ may cause an outward, repolarizing, shift in current during this phase of the action potential. The result will be accentuation of the action potential “notch” and in early repolarization of the epicardium that may be partial or complete.
On the 12-lead ECG these changes will be visible in the shape of the ST-segment. The type 2 and 3 or saddle shaped ST segment results from a more pronounced J wave that appears as a R' and because the epicardial action potential remains intact and shorter than the endocardial action potential there is a positive T wave. The type 1 or coved type ST-segment shows J wave elevation and a negative T wave because the epicardial action potential becomes longer than the endocardial resulting from delayed opening of calcium channels.

In summary the typical Brugada syndrome ECG ST shape results from the increase in transmural dispersion in repolarization.

Because of the dispersion in repolarization action potentials from sites where it is maintained can move to sites where early repolarization has occurred. Reactivation of ion channels may occur at these sites leading to the development of an extrasystole due to phase 2 reentry. When phase 2 reentry occurs a mechanism for development of arrhythmias is present. Phase 2 reentry may trigger a circus movement reentry which becomes apparent on the ECG as polymorphic ventricular tachycardia (VT) or ventricular fibrillation (VF).

### 3.1.7 Ionic mechanisms

Any reduction in depolarising ion current, \( I_{Na} \) or \( I_{Ca} \), or increase in repolarising ion current, \( I_{to} \), \( I_{Kr} \), \( I_{Ks} \), or \( I_{K-ATP} \) can be at the basis of the Brugada syndrome ECG. These changes could theoretically result from mutations in the genes encoding these ion channels or from mutations in genes encoding interacting proteins.\(^7\) Thusfar only mutations in the \( SCN5A \) gene affecting \( I_{Na} \) have been found to be involved\(^6\). These mutations have consistently shown to reduce available cardiac sodium current as mentioned previously\(^8\). The mechanism by which mutations are found to do so have been elucidated by expressing the mutated sodium channels in cellular expression models, usually mammalian HEK, cos or tsA cells or frog oocytes, and studying them using the patch clamp technique\(^8\). In these studies a reduction in sodium current has been shown to result from the reduction or complete absence of sodium channel expression or from changes in the kinetics of sodium channel gating that change channel conductance\(^8\).
Figure 3. (A) Shown is a schematic representation of the normal ECG in relationship to the endo-, mid- and epicardial action potentials. Note the difference in phase 1 between the action potentials which results from the differences in $I_{T_0}$ in the layers of the heart. (B) Shown is a schematic representation of the effects of a lower action potential upstroke during phase 0, due to a reduction in sodium current. The differences in repolarization between the epi- and endocardial layers may result in the ST-segment elevation and a positive or a negative T-wave. (adapted from: C. Antzelevitch, J. Fish. Electrical heterogeneity within the ventricular wall. Basic Res. Cardiol. 2001;96:517-527)

82
REFERENCES


